Hydrogen Sulfide in Cardiovascular Disease

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The cardiovascular system can be programmed by a diversity of early-life insults, leading to cardiovascular disease (CVD) in adulthood. This notion is now termed developmental origins of health and disease (DOHaD). Emerging evidence indicates hydrogen sulfide (H_2S), a crucial regulator of cardiovascular homeostasis, plays a pathogenetic role in CVD of developmental origins. Conversely, early H_2S-based interventions have proved beneficial in preventing adult-onset CVD in animal studies via reversing programming processes by so-called reprogramming.

hydrogen sulfide | cardiovascular disease | hypertension | atherosclerosis | cysteine | developmental origins of health and disease (DOHaD) | N-acetylcysteine

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide, accounting for almost one third of all global deaths [1]. CVD is a cluster of disorders of the heart and blood vessels and is comprised of coronary heart disease, peripheral vascular disease, cerebrovascular disease and other conditions. Although CVD is most common in older adults, atherosclerosis can begin in childhood and progress slowly across the life span [2]. Therefore, reducing the global burden of CVD by identifying children at risk and providing preventive interventions early are extremely important. Noteworthy, CVD can originate from the early stages of life, not only childhood but tracing back into the fetal life. This theory is now termed the developmental origins of health and disease (DOHaD) by observing how a suboptimal environment in utero has an adverse influence on offspring outcomes in later life [3].

The fetal cardiovascular system is vulnerable to adverse early-life environmental insults [4]. Developmental plasticity accommodates morphological and functional changes during organogenesis, leading to endothelial dysfunction, stiffer vascular tree, small coronary arteries, low nephron endowment, and fewer cardiomyocytes, through a process known as cardiovascular programming [4][5][6]. So far, several mechanisms underlying cardiovascular programming have been proposed, like oxidative stress, nitric oxide (NO) deficiency, activation of the renin–angiotensin system (RAS), dysregulated nutrient-sensing signals, and dysbiosis of gut microbiota [4][5][6].

Hydrogen sulfide (H_2S), the third gasotransmitter, has emerged as a crucial regulator of cardiovascular homeostasis [7][8][9]. H_2S exerts multifaceted biological functions, including vasodilatation, angiogenesis, antioxidant, anti-inflammation, mitochondria bioenergetics, and antiapoptosis [10][11]. In this regard, H_2S-releasing drugs have been considered as potential therapeutics for CVD [7][8]. It is noteworthy that the DOHaD concept provides a strategy termed reprogramming to reverse or postpone the programming processes in early life,

accordingly protecting offspring against many adult diseases of developmental origins [12]. Emerging evidence suggests that H_2S can be used as a reprogramming strategy in hypertension of developmental origins [13]. Although H_2S has been shown to have beneficial effects on CVD [7][8], whether it could serve as a reprogramming intervention for developmental origins of CVD remains largely unclear.

2. Hydrogen Sulfide in the Cardiovascular System

2.1. H_2S Signaling Pathway

H_2S, a colorless gas with a characteristic foul odor of rotten eggs, was first identified as an environmental toxin in the 1700s and opened three centuries of research into its biological roles [14]. In the late 1990s, H_2S was reclassified as the third gaseous signaling molecule, alongside nitric oxide (NO) and carbon monoxide (CO) [10]. Currently, H_2S is known as a ubiquitous second messenger molecule with important functions in cardiovascular physiology [10][15]. Much of the previous work investigating the actions of H_2S has been directly focused on incident CVD; however, there is a growing need to better understand the mechanisms and pathways of H_2S signaling in CVD of developmental origins.

Figure 1 illustrates three major pathways of H_2S synthesis, including enzymatic pathway, nonenzymatic pathway, and bacteria origins. Three enzymes have been identified to enzymatically generate H_2S, cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulphurtransferase (3MST) [10]. CBS and CSE are cytosolic enzymes, but 3-MST is mainly existing in the mitochondria. l-cysteine is the principal substrate for both CBS and CSE to generate H_2S. CBS and CSE can also produce H_2S using other substrates. Homocysteine can be catalyzed by CBS to generate cystathionine, followed by CSE to produce l-cysteine. All of the above-mentioned H_2S-generating enzymes are expressed in the heart and blood vessels [10][16]. In an alternative pathway, 3-mercaptopyruvate, the substrate for 3-MST to produce H_2S, is provided by cysteine aminotransferase (CAT) and D-amino acid oxidase (DAO). In the peroxisome, d-cysteine can be catabolized by DAO to generate H_2S [17]. Besides the enzymatic pathway, H_2S can be nonenzymatically produced through thiosulfate, glucose, polysulfides, glutathione, and elemental sulfur.

Another source of H_2S is coming from the gut microbiota. Approximately fifty percent of fecal H_2S is derived from bacteria. In the gut, sulfate-reducing bacteria (SRB) obtain energy from the oxidation of organic compounds, reducing sulfate to H_2S. *Desulfovibrio* account for 66% of all SRB in the human colon [18]. Other gut bacteria may also produce H_2S by sulfite reduction, including species *E. coli, Enterobacter, Salmonella, Klebsiella, Bacillus, Corynebacterium, Staphylococcus,* and *Rhodococcus* [19]. Conversely, sulfur-oxidizing bacteria (SOB) reduces H_2S via sulfur oxidation. The SOB members include genera *Acidithiobacillus*, *Bacillus*, *Paracoccus*, *Pseudomonas*, and *Xanthobacter*. In the gut, a huge quantity of H_2S is oxidized by colonocytes to thiosulfate. The existence of thiosulfate in cecal venous blood not only reflects the detoxification of H_2S but also the recycling of H_2S.

In the circulation and tissues, free H_2S can be scavenged and stored in the bound-sulfate and sulfane sulfur pools. Methylation and oxidation are two major mechanisms of H_2S metabolism. H_2S can be excreted in urine and flatus

as free sulfate, free sulfide or thiosulfate.

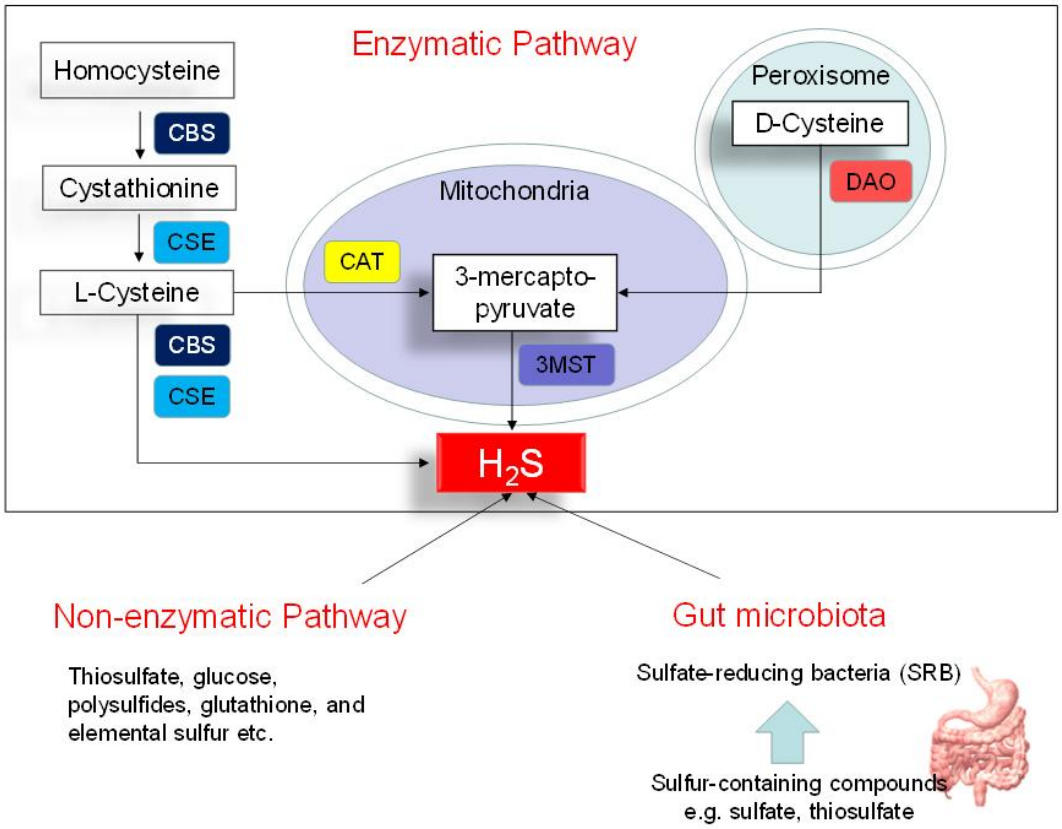

Figure 1. Schematic representation of three major sources of H_2S: enzymatic pathway, nonenzymatic pathway, and bacterial origins. Cystathionine β-synthase (CBS) catalyzes homocysteine to produce Cystathionine. Cystathionine γ-lyase (CSE) catalyzes cystathionine to form l-cysteine or l-cysteine to generate H_2S. 3-Mercaptopyruvate sulfurtransferase (3MST) produces H_2S from 3-mercaptopyruvate, which is generated by cysteine aminotransferase (CAT) and d-amino acid oxidase (DAO) from l-cysteine and d-cysteine, respectively. Another source of endogenous H_2S is coming from nonenzymatic processes. The other source of H_2S is derived from gut microbes, mainly by the sulfate-reducing bacteria (SRB).

2.2. The Role of H_2S in the Pathophysiology of CVD

Multiple lines of evidence indicate that H_2S plays a crucial role in the pathogenesis of CVD. The first are reports on knockout mice lacking genes encoding for CSE, CBS, and 3-MST. CSE is the most relevant H_2S-producing enzyme in the cardiovascular system. Mutant mice lacking CSE had decreased H_2S levels in the serum, heart, vessels, and other tissues [20]. CSE knockout mice displayed hypertension, endothelial dysfunction, and accelerated atherosclerosis [20][21]. CBS-deficient mice developed endothelial dysfunction [22] and cerebral vascular dysfunction [23]. 3-MST knockout mice developed hypertension and cardiac hypertrophy [17]. Second, are observations that impaired H_2S-generating pathways were found in CVDs, including atherosclerosis [24], coronary artery disease [25], stroke [26], and peripheral vascular disease [15].

Third, are studies of protein S-sulfhydration, a vital post-translational modification induced by H_2S [9]. S-sulfhydration usually increases the reactivity of target proteins via formation of a cysteine persulfide to target proteins [9]. H_2S is able to S-sulfhydrate Kelch-like ECH associated protein 1 (Keap1), specificity protein-1 (SP-1), nuclear factor kappa-B (NF-κB) and interferon regulatory factor-1 (IRF-1) to regulate target gene transcription, which is crucial for the regulation of endothelial phenotypes, myocardial hypertrophy, mitochondrial biogenesis, oxidative stress, apoptosis and inflammation [9].

Fourth, several H_2S-releasing drugs have demonstrated considerable promise for beneficial effects against CVDs in various animal models [7][8]. As reviewed elsewhere [7], several cytoprotective actions of H_2S have been reported in the heart and vasculature. In the heart, the protective effects of H_2S signaling was related to anti-inflammation, antiapoptosis, reduction of oxidative stress, and antifibrosis that leads to cardiac remodeling and functional improvements. In the vessels, H_2S signaling can preserve endothelial NO synthase (eNOS)-derived NO production, while reducing oxidative stress, inflammation, fibrosis, and smooth muscle cell proliferation.

2.3. H_2S Signaling in Various CVDs

Endothelial dysfunctions are associated with various CVDs, including hypertension, atherosclerosis, myocardial infarction, and the cardiovascular complications of diabetes. H_2S can prime endothelial cells toward angiogenesis and contribute to relax vascular smooth muscle cells, and thereby reducing BP [27]. A deficit in H_2S homeostasis is involved in the pathogenesis of endothelial dysfunction, while the application of H_2S-releasing drugs to increase endogenous H_2S level can restore endothelial function and antagonize the progression of CVDs.

Hypertension is a key risk factor for multiple CVDs. Like NO, H_2S is a vasodilator. H_2S has been reported to relax various blood vessels, such as the rat thoracic aorta, portal vein, and peripheral resistance vessels [28][29][30]. The involvement of H_2S deficiency in hypertension has been examined in various animal models of hypertension, including the spontaneously hypertensive rat (SHR) [31], the renovascular hypertensive model [32], Dahl salt-sensitive rats [33], and NO-deficient rats [34]. Conversely, several prior studies have shown the beneficial effects of exogenous and endogenous H_2S on hypertension, as reviewed elsewhere [35]. However, little is known about whether these H_2S-based therapies could be used as reprogramming interventions perinatally to reduce the vulnerability to developing cardiovascular programming in offspring.

ApoE knockout mice developed advanced atherosclerosis related to a decreased plasma H_2S level and vascular CSE expression/activity, suggesting disturbance of the vascular CSE/H2S pathway plays a role in the pathogenesis of atherosclerosis [36]. Additionally, a reduction in circulating H_2S has also been noted in diabetic animal models and diabetic patients [37]. Conversely, H2S therapy proved beneficial in diabetes-accelerated atherosclerosis in diabetic mice [38]. In a rat model of myocardial ischemia–reperfusion (I/R), pharmacologic inhibition of CSE resulted in an increase in infarct size, whereas H_2S replacement displayed myocardial protection [39]. Likewise, cardiac-specific overexpression of CSE in mice protects against myocardial I/R injury [40].

Summarizing, in clinical and preclinical studies of various CVDs, endogenous H_2S production is diminished in these pathological conditions and H_2S deficiency contributes to the progression of disease [7].

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